REMARKS

In view of the following Remarks, the Examiner is requested to withdraw the rejection and allow Claims 1, 5-8, 13, 17, and 27-33, the only claims pending and currently under examination in this application.

FORMAL MATTERS:

Claims 1, 6, 13, and 28-30 are amended. Support for these amendments may be found in the specification on page 16, lines 15-19.

Claims 11 and 13 are amended to correct the status identifiers. The Applicants thank the Examiner for pointing out these errors.

Claims 31-33 are added. Support for Claim 31 may be found in the specification, page 15, lines 1-4. Support for Claim 32 may be found in the specification, page 7, lines 26-29. Support for Claim 33 may be found in the specification, page 5, lines 2-6.

The specification has been amended to introduce a new Sequence Listing.

No new matter is added. As such, the Examiner is requested to enter the above amendments.

PRIORITY

The Examiner has asserted that the priority date of Claim 30, which recites SEQ ID NO:9, is determined to be 11/05/2003, the filing date of PCT/RU/00474, since the sequences disclosed in 60/425,570 filed 11/12/2002, are not the same as SEQ ID NO:9 of the instant application.

The Applicants respectfully submit that Claim 30 should be entitled to the priority date of 11/12/2002.

CERTIFICATION REGARDING SEQUENCE LISTING

I hereby certify that the enclosed Sequence Listing is being submitted under 37 CFR §§ 1.821(c) and (e) in paper and computer readable form (.TXT).

As required by 37 CFR 1.821(f), I hereby state that the content of the paper and computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(c) and (e) are the same. The Computer Readable Format (CRF), being submitted under 37 CFR §§ 1.52(e) and 1.824, is formatted on IBM-PC, the operating system compatibility is MS-Windows and the file listing is:

SeqList_amended 4-17-2009.doc 144KB created April 17, 2009.

I hereby certify that the enclosed submission includes no new matter. The Sequence Listing was prepared with the software PatentIn, and conforms to the Patent Office guidelines. Applicant respectfully submits that the subject application is in adherence to 37 CFR §§ 1.821-1.825.

CLAIM OBJECTIONS

The Examiner has objected to Claims 1, 28 and 30 for being drawn to a non-elected invention. Specifically, the Examiner states that Applicants have elected SEQ ID NO:10, which is encoded by SEQ ID NO:9 as the elected invention and as such, claim 1 and dependent claims 5, 6, 13, 17, 27, 28 and 30 are examined only to the extent that they read on a SEQ ID NO:10 which is encoded by EQ ID NO: 9. Applicants are required to delete the non-elected subject matter from the instant claims 1, 28 and 30.

The Applicants have amended these claims to remove the SEQ ID numbers that denote non-elected subject matter. Accordingly, this objection may be withdrawn.

REJECTIONS UNDER §112, ¶2

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner notes that Claim 29 recites dependence upon Claim 26, but that Claim 26 is cancelled.

The Applicants have amended Claim 29 to recite dependence upon Claim 1. In view of this amendment, reconsideration and withdrawal of the rejection is requested.

REJECTIONS UNDER §112, ¶1 – WRITTEN DESCRIPTION

Claims 1, 5-8, 13, 17, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 U.S.P.Q.2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

Newly amended Claim 1, upon which the pending claims depend, recites "an isolated nucleic acid molecule encoding a fluorescent protein, wherein said protein has at least 85% identity with full length SEQ ID NO:10." Accordingly, the nucleic acid sequences of the pending claims encode fluorescent proteins having a sequence identity of at least 85% with SEQ ID NO:10.

In establishing this rejection, the Examiner asserts that "the specification does not provide any information regarding the structure-function correlation of phiYFP in terms of which amino acids are necessary and sufficient for phiYFP to be a fluorescent protein" (p. 9, l. 1-3). Further, that "there is no evidence on the record of a relationship between the structure of any nucleic acid encoding a fluorescent protein and of the claimed nucleic acid molecules encoding a fluorescent protein with at least 85% identity with SEQ ID No. 10, over the entire length of SEQ ID No:10, that would provide any reliable information about the structure of other nucleic acids encoding a fluorescent protein within the genus." (p. 9, l. 7-12). Finally, that "the amino acids that are necessary and sufficient for phiYFP to be a fluorescent protein have not been disclosed and SEQ ID No. 9 encoding SEQ ID No. 10 was obtained by random mutagenesis." (p. 10, l. 9-11)

The Applicants submit that the specification in view of the art provides ample information regarding the structure-function correlation of the disclosed nucleic acids, the proteins they encode, and the amino acids that are necessary and sufficient for their fluorescence. The specification teaches the relevance of GFP and Anthozoan protein structure to the structure of the disclosed proteins (p. 1, l. 13-26; Figure 1). The art teaches a well-studied and highly predictable structure of GFP; see, for example, Yang et al. ((1996) Nat. Biotech 14:1246-51) (Exhibit A) and Ormo et al. ((1996) Science 273:1392-95) (Exhibit B). The art teaches that this structure is conserved amongst all fluorescent proteins and can be used to make predictions as to which amino acids can be substituted in these proteins and how without loss of protein function; see, for example, Matz et al. ((1999) Nat Biotech 17:969-973) (Exhibit C). Thus, one of ordinary skill in the art would understand from the specification that the proteins encoded by the claimed nucleic acids should have a structure resembling that of the well-studied and highly predictable structure of GFP while maintaining at least 85% identity with SEQ ID NO:10. For example, the specification and the art teach the reliance of GFP and Anthozoan proteins upon their fluorophore for their fluorescence character (specification, p. 1, l. 27-31; Matz et al.). The

specification teaches that the proteins encoded by the claimed nucleic acids also rely upon a fluorophore for their fluorescent character: "fluorescent characteristic . . . arises from the interaction of two or more amino acid residues of the protein and not from a single amino acid residue." (p. 5, l. 2-4). Thus, the artisan would understand that the amino acid residues that comprise the fluorophore in the disclosed proteins should be conserved, and would know how to use publicly available web-based software such as Clustal W to align these protein sequences and identify these amino acid residues.

Furthermore, the specification teaches 7 examples of proteins that are encoded by nucleic acids of the claimed genus (SEQ ID NOs:2, 4, 6, 8, 10, 18 and 20) and 2 examples of proteins from other species (SEQ ID NOs:12 and 14) that could be aligned with GFP so as to identify all of the residues that should be conserved to maintain fluorescence activity. Indeed, the specification provides teachings of how to perform such alignments; see Figure 1. The Applicants submit that one of ordinary skill in the art would be able to use this alignment in Figure 1 as well as alignments with other GFP-like proteins know in the art to identify the amino acids to be conserved, for example, the amino acids comprising the fluorophore, so as to retain the fluorescence character of the protein. Moreover, such alignments would demonstrate to the artisan that the disclosed proteins share only 12.8% conserved amino acids with GFP and one another (see Exhibit D, which is an alignment of the disclosed proteins to one another and to GFP; asterisks indicate conserved amino acids); accordingly, the artisan would also recognize from such alignments that strict conservation of most amino acids of these proteins is not required to maintain protein function. Thus, the specification provides sufficient written description such that one of ordinary skill in the art would know that a high degree of amino acid substitution could be tolerated by the proteins of this family including the protein encoded by SEQ ID NO:10 without loss of fluorescence, and would be able to determine which amino acid substitutions those would be.

In support of this expectation that a high degree of amino acid substitutions in these proteins can be tolerated without losing protein function, the art teaches a plethora of GFP mutations that preserve GFP fluorescence activity. For example, Heim et al. ((1996) Current Biol. 6:178-182) (Exhibit E) teaches six mutants comprising mutations in 10 residues of GFP (Table 1). Siemering et al. ((1996) Current Biol. 6(12):1653-63) (Exhibit F) teaches seven additional mutants (mgfp4, mgfpB, mgfpA, mgfp5, mgfp4 + Y66H, mgfpA + Y66H) comprising mutations in another three residues. Yang et al. ((1998) J Biol Chem 273(14):8212-8216)

(Exhibit G) teaches two additional mutants comprising mutations in an additional two residues. In addition, the art teaches a plethora of other fluorescent proteins having minimal identity with GFP. For example, Wiedenmann et al. ((2000) PNAS 97(26):14091-6) (Exhibit H) teaches three fluorescent proteins of *Anemonia sulcata* (asFP499, asFP522, asFP595; see Table 1) that, as a group, share only 12.6% identity to GFP (see Figure 5, "consensus" line). Matz et al. (Exhibit C) teaches six fluorescent proteins from Anthozoa that, as a group, share only 11% identity with GFP (see Figure 1, "cns. All" line), and how the fluorescence activity of GFP and other fluorescent proteins relies upon these conserved residues. Bevis et al. ((2002) Nat. Biotechnol 20(1):83-7) (Exhibit I) teaches 7 mutants of one of these Anthozoan proteins, dsRed, (N42H, N42Q, DsRed1, dsRed2, DsRed.T1, DsRed.T3, DsRed.T4; see p. 83, col. 2, para. 3-4, p. 84, Table 1), all of which retain fluorescent activity. Campbell et al. ((2002) PNAS 99(12):7877-82) (Exhibit J) teaches 4 more mutants of dsRed (I125R, dimer2, tdimer2, mRFP1; see paragraph bridging pages 7878-9, and Table 1) that retain fluorescent activity. Shaner et al. ((2004) Nat Biotechnol 22(12):1567-72) (Exhibit K) teaches a multitude more dsRed-based mutants with improved extinction coefficients, photostability, and a variety of fluorescence spectra (see, for example, Table 1).

Thus, the artisan would find a wealth of examples in the specification and the art which teach that SEQ ID NO:10 can tolerate a high degree of amino acid substitution while still retaining fluorescence activity. Furthermore, the artisan would recognize that they could use alignments of the proteins provided in the specification with those provided in the art to identify exactly <u>which</u> amino acids of SEQ ID NO:10 are conserved and should not be mutated versus those which are not conserved and could be mutated so as to retain fluorescence activity. Moreover, the specification teaches methods of testing these predictions, by teaching methods of making mutant nucleic acids encoding mutant proteins (p. 8, l. 21-p. 9, l. 9; see also p. 26, l. 8-11), and of testing these mutant nucleic acid, for example by transfecting the nucleic acids into cells in culture, waiting 20 hours, and imaging the cells on a fluorescence microscope (p. 29, l. 7-16). Accordingly, the Applicants submit that the specification in view of the art provides a reasonable amount of teachings on the structure of wild type and mutant nucleic acid sequences that encode fluorescent proteins so as to provide sufficient written support for the genus of nucleic acids encoding mutants of SEQ ID NO:10 having a sequence identity of at least 85% with SEQ ID NO:10 that are encompassed by the pending claims.

In establishing this rejection, the Examiner also asserts that "The specification only discloses an example (a species) of various conditions that Applicant regards as 'stringent conditions.' The art recognizes that 'hybridization under stringent conditions' is determined by variations in multiple factors (detergents, salts, hydrogen bond competitor, and temperatures etc.). Therefore, the genus encompassed by 'hybridization under stringent conditions' is not described to render a skilled artisan to possess the sequences by hybridization that encodes a fluorescent protein having at least 85% identity with SEQ ID No.10." (p. 10, l. 19-21)

The Applicants submit that they have provided several methods for hybridizing under stringent conditions at, for example, page 8, lines 7-20. The methods provided include particular temperatures and buffer concentrations for hybridizing and washing, thereby providing the ordinary skilled artisan with very specific instructions for how to make and use the invention. Furthermore, as suggested by the Examiner, the art of hybridizing nucleic acids is very well-developed; accordingly, one of ordinary skill in the art would have a good understanding of how to perform these experiments based upon the temperatures and buffer concentrations provided and therefore how to make and use the present invention. Accordingly, one of ordinary skill in the art would find the provided written description to be sufficient so as to reasonably conclude that the inventor had possession of the claimed invention.

Thus, the Applicants submit that they have provided a written description such the one of ordinary skill in the art would reasonably conclude that the inventor had possession of the claimed invention. Reconsideration and withdrawal of the rejection is requested.

REJECTIONS UNDER §112, ¶1 - ENABLEMENT

Claims 1, 5-8, 13, 17, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, which being enabling for an isolated nucleic acid molecule comprising SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID NO. 10, and a vector/cell/kit comprising SEQ ID NO. 9 that encodes a fluorescent protein consisting of SE ID No. 10, allegedly does not reasonably provide enablement for (1) any isolated nucleic acid molecule encoding a fluorescent protein other than SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, or (2) any vector/cell/kit comprising any isolated nucleic acid molecule encodes a fluorescent protein other than SEQ ID NO 9 that encodes a fluorescent protein consisting of SEQ ID No. 10.

With respect to enablement, courts have held that: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

In making this rejection, the Examiner has applied the criteria set forth in *Wands*. In particular, the Examiner has focused on the breadth of the claimed genus of subject nucleic acids, and the support of this breadth as provided by the working examples and guidance provided by the specification and the level of predictability in the art.

However, the Applicants respectfully submit that in making this rejection, the Examiner has focused on the general art of protein structure and function rather than on the more relevant art of protein structure and function as it pertains to fluorescent proteins from Hydrozoas. As discussed below, the Applicants submit that there exists relevant art that demonstrates a well-developed understanding of the structure of these proteins and how changes to structure impact protein function. As such, the art establishes a precedent for extrapolation without undue experimentation from the examples presented in the pending application to the claimed genus of nucleic acids.

Breadth of the claims

Newly amended Claim 1, upon which the pending claims depend, recites "an isolated nucleic acid molecule encoding a fluorescent protein, wherein said protein has at least 85% identity with full length SEQ ID NO:10." Accordingly, the nucleic acid sequences of the pending claims encode fluorescent proteins having a sequence identity of at least 85% with SEQ ID NO:10.

In making this rejection, the Examiner asserts that "The breadth of the claims encompasses any isolated nucleic acid molecule encoding a fluorescent protein in addition to SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No.10, and any vector/cell/kit comprising any isolated nucleic acid molecule encoding a fluorescent protein in

addition to SEQ ID No. 9 encoding a fluorescent protein consisting of SEQ ID No.10." (p. 12, l. 17-21).

The Applicants submit that, contrary to the Examiner's assertions, and as discussed above, the nucleic acids of the pending claims are limited to those that encode fluorescent proteins having a sequence identity of at least 85% with SEQ ID NO:10. Accordingly, the claims are not unduly broad.

Guidance and working examples provided

"The Examiner asserts that the specification does not provide any guidance regarding the structure-function correlation of phiYFP in terms of which amino acids are necessary and sufficient for phiYFP to be a fluorescent protein. It would require undue experimentation for an artisan to determine which amino acids are necessary and sufficient for phiYFP-M1 (i.e. the claims SEQ ID No.10) to be a fluorescent protein to support the breadth of the claims." (p. 13, l. 10-14)

The Applicants submit that the specification in view of the art teaches a wealth of guidance and working examples that the ordinary skilled artisan would be able use to determine which amino acids are necessary and sufficient in SEQ ID No.10 to maintain fluorescence so as to identify other nucleic acids of the claimed genus.

The Applicants submit that the specification teaches 7 examples of proteins (SEQ ID NOs:2, 4, 6, 8, 10, 18 and 20) having a sequence identity of at least 85% with SEQ ID NO:10. Methods of identifying wild type proteins having a sequence identity of at least 85% with a known protein, for example, degenerate PCR and BLAST searching, are well understood in the art, and thus, one of ordinary skill in the art would know how to identify other nucleic acid sequences that encoding wild type fluorescent proteins having a sequence identity of at least 85% with SEQ ID NO:10. Additionally, the degeneracy of the genetic code is well understood in the art, and thus, one of ordinary skill in the art would know how to design a multitude of other nucleic acid sequences that would also encode these wild type fluorescent proteins. Accordingly, the Applicants submit that they have provided a reasonable number of examples of nucleic acid sequences that encode fluorescent proteins so as to support the species of wild type nucleic acids encompassed by the claimed genus.

Furthermore, the Applicants submit that, in view of the art, they have also provided sufficient guidance and written examples to enable the species of nucleic acids encoding mutants of wild type fluorescent proteins encompassed by the claimed genus. The specification teaches the relevance of GFP and Anthozoan protein structure to the structure of the disclosed proteins (p. 1, l. 13-26; Figure 1). The art teaches a well-studied and highly predictable structure of GFP; see, for example, Yang et al. (Exhibit A) and Ormo et al. (Exhibit B). The art teaches that this structure is conserved amongst all fluorescent proteins and can be used to make predictions as to which amino acids can be substituted in these proteins and how without loss of protein function; see, for example, Matz et al. (Exhibit C). Thus, one of ordinary skill in the art would know from the specification that the proteins encoded by the claimed nucleic acids should have a structure resembling that of the well-studied and highly predictable structure of GFP while maintaining at least 85% identity with SEQ ID NO:10. For example, the specification and the art teaches the reliance of GFP and Anthozoan proteins upon their fluorophore for their fluorescence character (specification, p. 1, l. 27-31; Matz et al.). The specification teaches that the proteins encoded by the claimed nucleic acids also rely upon a fluorophore for their fluorescent character: "fluorescent characteristic . . . arises from the interaction of two or more amino acid residues of the protein and not from a single amino acid residue." (p. 5, l. 2-4). Thus, the artisan would understand that the amino acid residues that comprise the fluorophore in the disclosed proteins should be conserved, and would know how to use publicly available web-based software such as Clustal W to align these protein sequences and identify these amino acid residues.

Indeed, in addition to providing 7 examples of proteins that are encoded by nucleic acids of the claimed genus, the specification provides 2 examples of proteins from other species (SEQ ID NOs:12 and 14) that could be aligned with GFP and with the 7 proteins encoded by the nucleic acids of the claimed genus so as to identify all of the residues that should be conserved to maintain fluorescence activity. In fact, the specification provides an example of how to perform such alignments; see Figure 1. The Applicants submit that one of ordinary skill in the art would know how to use the alignment in Figure 1 as well as alignments with other GFP-like proteins know in the art to identify the amino acids to be conserved, for example, the amino acids comprising the fluorophore, so as to retain the fluorescence character of the protein. More importantly, such alignments would demonstrate to the artisan that the disclosed proteins share only 12.8% conserved amino acid residues with GFP and one another (see Exhibit D, which is an alignment of the disclosed proteins to one another and to GFP); accordingly, the

artisan would also recognize from such alignments that strict conservation of most amino acids of these proteins is not required to maintain protein function. Thus, the specification provides sufficient guidance and working examples such that one of ordinary skill in the art would know that a high degree of amino acid substitution could be tolerated by the proteins of this family including protein encoded by SEQ ID NO:10 without loss of fluorescence, and would be able to determine which amino acid substitutions those would be.

In support of this expectation that a high degree of amino acid substitutions in these proteins can be tolerated without losing protein function, the art teaches a plethora of GFP mutations that preserve GFP fluorescence activity. For example, Heim et al. (Exhibit E) teaches six mutants comprising mutations in 10 residues of GFP (Table 1). Siemering et al. (Exhibit F) teaches seven additional mutants (mgfp4, mgfpB, mgfpA, mgfp5, mgfp4 + Y66H, mgfpA + Y66H) comprising mutations in another three residues. Yang et al. (Exhibit G) teaches two additional mutants comprising mutations in an additional two residues. The art also teaches a plethora of other fluorescent proteins having minimal identity with GFP. For example, Wiedenmann et al. (Exhibit H) teaches three fluorescent proteins of *Anemonia sulcata* (asFP499, asFP522, asFP595; see Table 1) that, as a group, share only 12.6% identity to GFP (see Figure 5, "consensus" line). Matz et al. (Exhibit C) teaches six fluorescent proteins from Anthozoans that, as a group, share only 11% identity with GFP (see Figure 1, "cns. All" line), and how the fluorescence activity of GFP and other fluorescent proteins relies upon these conserved residues. Bevis et al. (Exhibit I) teaches 7 mutants of one of these Anthozoan proteins, dsRed, (N42H, N42Q, DsRed1, dsRed2, DsRed.T1, DsRed.T3, DsRed.T4; see p. 83, col. 2, para. 3-4, p. 84, Table 1), all of which retain fluorescent activity. Campbell et al. (Exhibit J) teaches 4 more mutants of dsRed (I125R, dimer2, tdimer2, mRFP1; see paragraph bridging pages 7878-9, and Table 1) that retain fluorescent activity. Shaner et al. (Exhibit K) teaches a multitude more dsRed-based mutants with improved extinction coefficients, photostability, and a variety of fluorescence spectra (see, for example, Table 1).

Thus, the artisan would find a wealth of guidance and working examples in the specification and the art which teach that SEQ ID NO:10 can tolerate a high degree of amino acid substitution while still retaining fluorescence activity. Furthermore, the artisan would recognize that they could use alignments of the proteins provided in the specification with those provided in the art to identify exactly <u>which</u> amino acids of SEQ ID NO:10 are conserved and should not be mutated versus those which are not conserved and could be mutated so as to

retain fluorescence activity. Moreover, the specification teaches methods of testing these predictions, by teaching methods of making mutant nucleic acids encoding mutant proteins (p. 8, l. 21-p. 9, l. 9; see also p. 26, l. 8-11), and of testing these mutant nucleic acid, for example by transfecting the nucleic acids into cells in culture, waiting 20 hours, and imaging the cells on a fluorescence microscope (p. 29, l. 7-16). Accordingly, the Applicants submit that the specification in view of the art provides a reasonable amount of guidance and working examples on the relationship between the structure of the disclosed proteins and their function as fluorescent molecules that one of ordinary skill in the art would be able to identify other species of the claimed genus without undue experimentation.

State of the art, level of predictability in the art

The Examiner asserts that "in the art, it is unpredictable how variations of sequences in a given fluorescent protein would affect its function as a fluorescent protein. For instance, Shagin et al. teaches that homologs of the green fluorescent protein, including the recently described GFP-like domains of certain extracellular matrix proteins in Bilaterian organism, are remarkably similar at the protein level, yet they often perform totally unrelated functions, thereby warranting recognition as a superfamily." (p. 13, l. 15-10)

The Applicants submit that the pending claims do not recite limitations on protein function other than that the encoded proteins have a fluorescence activity. Accordingly, Shagin et al.'s teachings of how proteins of similar 3D-structures may perform totally unrelated functions from one another are not relevant to the pending claims. These extracellular matrix proteins in Bilaterian organism (nidogens) are not fluorescent proteins and share very slight homology at the protein level with GFP-like domains, however they form similar beta-can structure (clearly homologous fold) revealed by crystallographic studies. In contrary to Examiner note, Shagin et al. teaches that fluorescent proteins and nidogens are two clearly definable protein families where the first includes fluorescent and/or colored proteins capable of synthesizing the chromophore autocatalytically, while the second consists of G2FP domains, which are incapable of autocatalytic chromophore synthesis.

Rather, what <u>is</u> relevant is the state of the art and the level of predictability in the art regarding the structure of the claimed proteins and their function as fluorescent proteins. The Applicants submit that the state of the art pertaining to the relationship between structure and fluorescence activity of the family of proteins that is the subject matter of the pending claims is

well-developed, and as such, provides for a high degree of predictability. For example, as discussed above, Yang et al. (Exhibit A) and Ormo et al. (Exhibit B) teach a well-defined and highly predictable structure for GFP and other members of this family of proteins. Heim et al. (Exhibit E), Siemering et al. (Exhibit F), and Yang et al. (Exhibit G), discussed above, teach a number of mutants of GFP that retain fluorescence activity. Wiedenmann et al. (Exhibit H), Matz et al. (Exhibit C), Bevis et al. (Exhibit I), Campbell et al. (Exhibit J), and Shaner et al. (Exhibit K), discussed above, teach a wealth of fluorescent proteins from non-bioluminescent species that share minimal identity with GFP, and in some cases with their wild type 'parents', but retain fluorescence due to a few conserved residues. Thus, the state of the art with regard to the structure-function relationship of proteins of the claimed subject matter and the impact that structural mutations will have on their function is relatively well-developed.

Additionally, the specification teaches methods of testing these predictions which are also well-developed, as these methods rely upon the highly predictable arts of DNA manipulation, nucleic acid expression, protein characterization, and microscopy. Thus, the state of the art with regard to validating predictions of which changes to structure will impact these proteins' function is also well-developed.

Thus, the Applicants submit that the state of the relevant art with regard to predicting and validating the residues of fluorescent proteins from proteins having 85% identity to SEQ ID NO:10 that may be mutated while retaining fluorescence activity is well-developed. Likewise, the art with regard to predicting and validating the residues of chromo- and fluorescent proteins having 85% identity to SEQ ID NO:10 that can be mutated so as to retain fluorescent activity is highly predictable.

Therefore, the Applicants submit the guidance and working examples provided by the specification and the art in view of the well developed state of the relevant art and the high level of predictability in the art provide suitable support for the claimed breadth, and that, as such, one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. In view of these remarks, reconsideration and withdrawal of the rejection is requested.

REJECTIONS UNDER §102

Claims 1, 5-8, 13, 17, and 27-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Baubet et al. (Baubet et al. US 2008/0213879, publication date 09/04/2008, Division of US 6,936,475, which is a Continuation of PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987).

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.,* 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert denied*, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

Newly amended Claim 1, upon which the pending claims depend, recites "a fluorescent protein, wherein said protein has at least 85% identity with full length SEQ ID NO:10." The Applicants submit that Baubet et al. do not teach this claim element because Baubet et al. teach proteins that have, at most, 50.5% identity with full length SEQ ID NO:10; see, for example, the alignments provided by the Examiner, pages 16-20 of the Office Action.

In making this rejection, the Examiner asserts that "Claim 1 reads on any isolated nucleic acid molecule comprising nucleotide sequences, which encodes a fluorescent protein having amino acid sequences that have at least 85% identity of any fragment of SEQ ID No.10." (p. 14, l. 25 – p. 15, l. 2).

The Applicants submit that newly amended Claim 1 recites that the sequences have at least 85% identity with full length SEQ ID NO:10, and that, as such, Baubet et al. do not teach this claim element. Accordingly, Baubet et al. do not anticipate Claim 1 or its dependents.

In making this rejection, the Examiner also asserts that, with regard to Claim 13, the limitation of 'at least 300 residues in length of the nucleic acid molecule' reads on those identical sequences that are not necessarily continuous." (p. 15, l. 11-15)

Claim 13 recites "A nucleic acid molecule having a sequence that is substantially the same as, or identical to a nucleotide sequence of at least 300 nucleotides in length of the nucleic acid molecule according to claim 1." Thus, what is claimed is a nucleic acid molecule having a sequence that is substantially the same as, or identical to, a nucleotide sequence <u>of at least 300 nucleotides in length of a nucleic acid molecule that encodes a protein having 85% identity with SEQ ID NO:10</u>. The Applicants submit that for such to be the case, the nucleic acid molecule of claim 13 must have its nucleotides in the same sequence as the nucleic acid molecule of claim 1. Accordingly, contrary to the Examiner's assertions, the claim does <u>not</u> read on identical sequence that are not necessarily continuous. Furthermore, the Applicants submit that Baubet et al. do not teach this claim element because Baubet et al. teach nucleic acid sequence that has, at most, 47.1% identity with a nucleotide sequence of at least 300 contiguous nucleotides in length that encode a protein having at least 85% identity with full length SEQ ID NO:10; see, for example, the alignments provided by the Examiner, pages 20-26 of the Office Action. As such, Baubet does not teach pending Claim 13, and thus does not anticipate the pending claims.

In view of the claim amendments and remarks above, reconsideration and withdrawal of the rejection is requested.

Claims 1, 5-8, 13, 17, and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Baubet et al. (PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001).

As discussed above, newly amended Claim 1, upon which the pending claims depend, recites "a fluorescent protein, wherein said protein has at least 85% identity with <u>full length</u> SEQ ID NO:10." The Applicants submit that Baubet et al. do not teach this claim element because Baubet et al. teach proteins that have, at most, 50.5% identity with full length SEQ ID NO:10; see, for example, the alignments provided by the Examiner, pages 16-20 of the Office Action.

In making this rejection, the Examiner asserts that "Claim 1 reads on any isolated nucleic acid molecule comprising nucleotide sequences, which encodes a fluorescent protein

having amino acid sequences that have at least 85% identity of any fragment of SEQ ID No.10." (p. 26, l. 9-11). The Applicants submit that newly amended Claim 1 recites that the sequences have at least 85% identity with full length SEQ ID NO:10, and that, as such, Baubet et al. do not teach this claim element. Accordingly, Baubet et al. do not anticipate Claim 1 or its dependents.

In making this rejection, the Examiner also asserts that, with regard to Claim 13, the limitation of 'at least 300 residues in length of the nucleic acid molecule' reads on those identical sequences that are not necessarily continuous." (p. 27, l. 5-7)

As discussed above, Claim 13 recites "A nucleic acid molecule having a sequence that is substantially the same as, or identical to a nucleotide sequence of at least 300 nucleotides in length of the nucleic acid molecule according to claim 1." Thus, what is claimed is a nucleic acid molecule having a sequence that is substantially the same as, or identical to, a nucleotide sequence of at least 300 nucleotides in length of a nucleic acid molecule that encodes a protein having 85% identity with SEQ ID NO:10. The Applicants submit that for such to be the case, the nucleic acid molecule of claim 13 must have its nucleotides in the same sequence as the nucleic acid molecule of claim 1. Accordingly, contrary to the Examiner's assertions, the claim does not read on identical sequence that are not necessarily continuous. Furthermore, the Applicants submit that Baubet et al. do not teach this claim element because Baubet et al. teaches nucleic acid sequence that has, at most, 47.1% identity with a nucleotide sequence of at least 300 contiguous nucleotides in length that encode a protein having at least 85% identity with full length SEQ ID NO:10; see, for example, the alignments provided by the Examiner, pages 20-26 of the Office Action. As such, Baubet does not teach pending Claim 13, and thus does not anticipate the pending claims.

In view of the claim amendments and remarks above, reconsideration and withdrawal of the rejection is requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 12-0425.

Respectfully submitted,

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